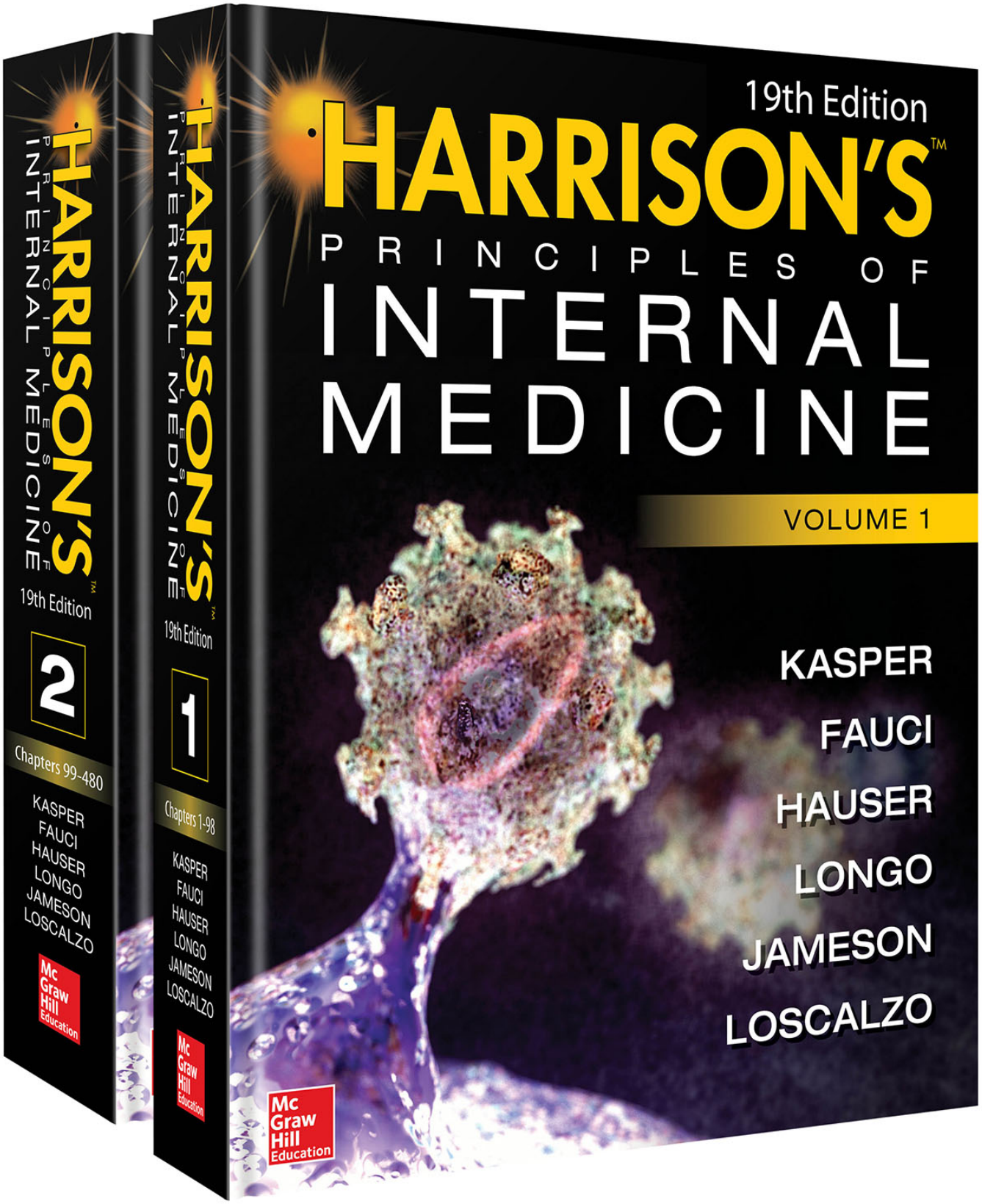
HARRISON'S
PRINCIPLES OF
INTERNAL MEDICINE
19th Edition
2
Chapters 99-480
KASPER
FAUCI
HAUSER
LONGO
JAMESON
LOSCALZO
Mc Graw Hill Education
HARRISON'S
PRINCIPLES OF
INTERNAL MEDICINE
19th Edition
1
Chapters 1-98
KASPER
FAUCI
HAUSER
LONGO
JAMESON
LOSCALZO
Mc Graw Hill Education
19th Edition
HARRISON'S™
PRINCIPLES OF
INTERNAL MEDICINE
VOLUME 1
KASPER
FAUCI
HAUSER
LONGO
JAMESON
LOSCALZO
Mc Graw Hill Education

PROGNOSIS

FUO-related mortality rates have continuously declined over recent decades. The majority of fevers are caused by treatable diseases, and the risk of death related to FUO is, of course, dependent on the underlying disease. In a study by our group (Table 26-1), none of 37 FUO patients without a diagnosis died during a follow-up period of at least 6 months; 4 of 36 patients with a diagnosis died during follow-up due to infection (n = 1) or malignancy (n = 3). Other studies have also shown that malignancy accounts for most FUO-related deaths. Non-Hodgkin's lymphoma carries a disproportionately high death toll. In nonmalignant FUO, fatality rates are very low. The good outcome in patients without a diagnosis confirms that potentially lethal occult diseases are very unusual and that empirical therapy with antibiotics, antituberculous agents, or glucocorticoids is rarely required in stable patients. In less affluent regions, infectious diseases are still a major cause of FUO, and outcomes may be different.

SECTION 3 NERVOUS SYSTEM DYSFUNCTION

27 Syncope

Roy Freeman

Syncope is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow. The onset is rapid, duration brief, and recovery spontaneous and complete. Other causes of transient loss of consciousness need to be distinguished from syncope; these include seizures, vertebrobasilar ischemia, hypoxemia, and hypoglycemia. A syncopal prodrome (*presyncope*) is common, although loss of consciousness may occur without any warning symptoms. Typical presyncopal symptoms include dizziness, lightheadedness or faintness, weakness, fatigue, and visual and auditory disturbances. The causes of syncope can be divided into three general categories: (1) neurally mediated syncope (also called *reflex or vasovagal syncope*), (2) orthostatic hypotension, and (3) cardiac syncope.

Neurally mediated syncope comprises a heterogeneous group of functional disorders that are characterized by a transient change in the reflexes responsible for maintaining cardiovascular homeostasis. Episodic vasodilation (or loss of vasoconstrictor tone) and bradycardia occur in varying combinations, resulting in temporary failure of blood pressure control. In contrast, in patients with orthostatic hypotension due to autonomic failure, these cardiovascular homeostatic reflexes are chronically impaired. Cardiac syncope may be due to arrhythmias or structural cardiac diseases that cause a decrease in cardiac output. The clinical features, underlying pathophysiologic mechanisms, therapeutic interventions, and prognoses differ markedly among these three causes.

EPIDEMIOLOGY AND NATURAL HISTORY

Syncope is a common presenting problem, accounting for approximately 3% of all emergency room visits and 1% of all hospital admissions. The annual cost for syncope-related hospitalization in the United States is ~$2.4 billion. Syncope has a lifetime cumulative incidence of up to 35% in the general population. The peak incidence in the young occurs between ages 10 and 30 years, with a median peak around 15 years. Neurally mediated syncope is the etiology in the vast majority of these cases. In elderly adults, there is a sharp rise in the incidence of syncope after 70 years.

In population-based studies, neurally mediated syncope is the most common cause of syncope. The incidence is slightly higher in females than males. In young subjects, there is often a family history in first-degree relatives. Cardiovascular disease due to structural disease or arrhythmias is the next most common cause in most series, particularly in emergency room settings and in older patients. Orthostatic hypotension also increases in prevalence with age because of the reduced baroreflex responsiveness, decreased cardiac compliance, and attenuation of the vestibulosympathetic reflex associated with aging. In the elderly, orthostatic hypotension is substantially more common in institutionalized (54–68%) than community-dwelling (6%) individuals, an observation most likely explained by the greater prevalence of predisposing neurologic disorders, physiologic impairment, and vasoactive medication use among institutionalized patients.

TABLE 27-1 HIGH-RISK FEATURES INDICATING HOSPITALIZATION OR INTENSIVE EVALUATION OF SYNCOPE

Chest pain suggesting coronary ischemia
Features of congestive heart failure
Moderate or severe valvular disease
Moderate or severe structural cardiac disease
Electrocardiographic features of ischemia
History of ventricular arrhythmias
Prolonged QT interval (>500 ms)
Repetitive sinoatrial block or sinus pauses
Persistent sinus bradycardia
Bi- or trifascicular block or intraventricular conduction delay with QRS duration≥120 ms
Atrial fibrillation
Nonsustained ventricular tachycardia
Family history of sudden death
Preexcitation syndromes
Brugada pattern on ECG
Palpitations at time of syncope
Syncope at rest or during exercise

The prognosis after a single syncopal event for all age groups is generally benign. In particular, syncope of noncardiac and unexplained origin in younger individuals has an excellent prognosis; life expectancy is unaffected. By contrast, syncope due to a cardiac cause, either structural heart disease or primary arrhythmic disease, is associated with an increased risk of sudden cardiac death and mortality from other causes. Similarly, mortality rate is increased in individuals with syncope due to orthostatic hypotension related to age and the associated comorbid conditions (Table 27-1).

PATHOPHYSIOLOGY

The upright posture imposes a unique physiologic stress upon humans; most, although not all, syncopal episodes occur from a standing position. Standing results in pooling of 500–1000 mL of blood in the lower extremities and splanchnic circulation. There is a decrease in venous return to the heart and reduced ventricular filling that result in diminished cardiac output and blood pressure. These hemodynamic changes provoke a compensatory reflex response, initiated by the baroreceptors in the carotid sinus and aortic arch, resulting in increased sympathetic outflow and decreased vagal nerve activity (Fig. 27-1). The reflex increases peripheral resistance, venous return to the heart, and cardiac output and thus limits the fall in blood pressure. If this response fails, as is the case chronically in orthostatic hypotension and transiently in neurally mediated syncope, cerebral hypoperfusion occurs.

Syncope is a consequence of global cerebral hypoperfusion and thus represents a failure of cerebral blood flow autoregulatory mechanisms.

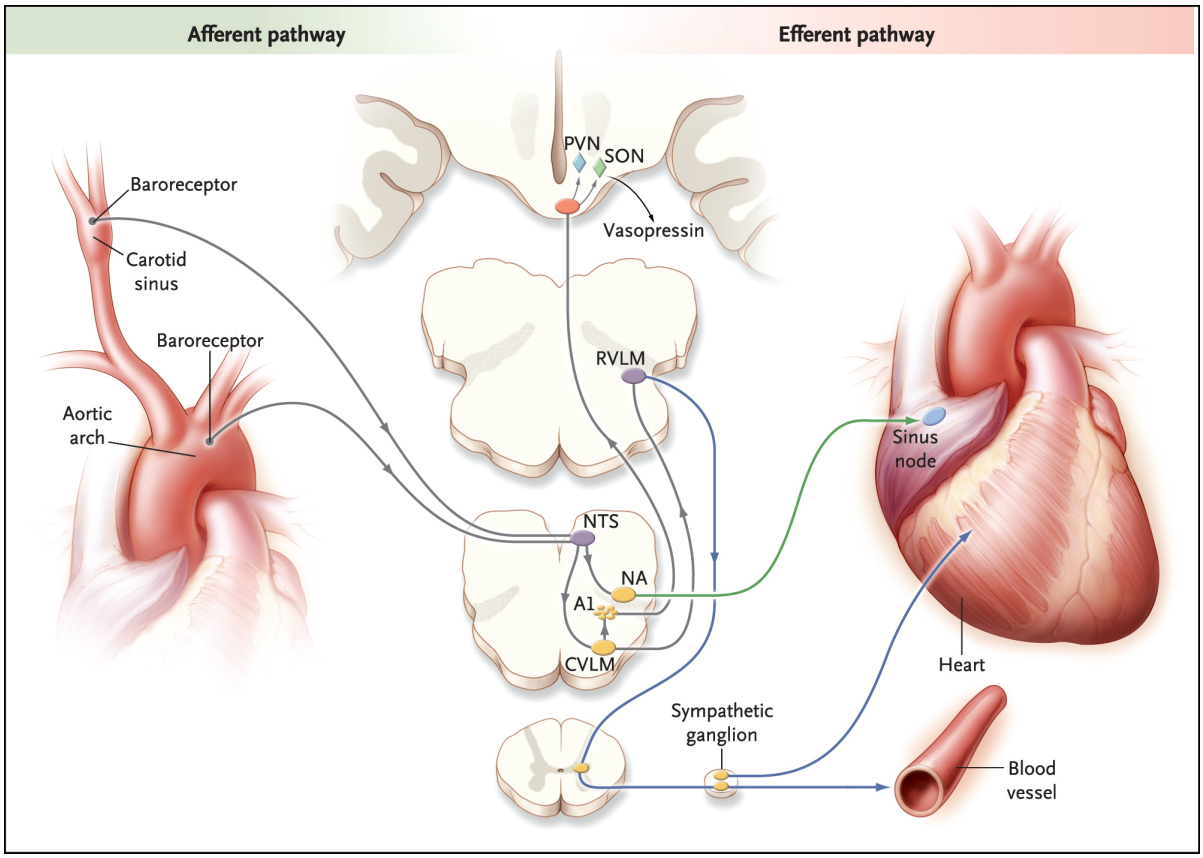

FIGURE 27-1 **The baroreflex.** A decrease in arterial pressure unloads the baroreceptors—the terminals of afferent fibers of the glossopharyngeal and vagus nerves—that are situated in the carotid sinus and aortic arch. This leads to a reduction in the afferent impulses that are relayed from these mechanoreceptors through the glossopharyngeal and vagus nerves to the nucleus of the tractus solitarius (NTS) in the dorsomedial medulla. The reduced baroreceptor afferent activity produces a decrease in vagal nerve input to the sinus node that is mediated via connections of the NTS to the nucleus ambiguus (NA). There is an increase in sympathetic efferent activity that is mediated by the NTS projections to the caudal ventrolateral medulla (CVLM) (an excitatory pathway) and from there to the rostral ventrolateral medulla (RVLM) (an inhibitory pathway). The activation of RVLM presympathetic neurons in response to hypotension is thus predominantly due to disinhibition. In response to a sustained fall in blood pressure, vasopressin release is mediated by projections from the A1 noradrenergic cell group in the ventrolateral medulla. This projection activates vasopressin-synthesizing neurons in the magnocellular portion of the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. *Blue* denotes sympathetic neurons, and *green* denotes parasympathetic neurons. *(From R Freeman: N Engl J Med 358:615, 2008.)*

Myogenic factors, local metabolites, and to a lesser extent autonomic neurovascular control are responsible for the autoregulation of cerebral blood flow (Chap. 330). The latency of the autoregulatory response is 5–10 s. Typically cerebral blood flow ranges from 50 to 60 mL/min per 100 g brain tissue and remains relatively constant over perfusion pressures ranging from 50 to 150 mmHg. Cessation of blood flow for 6–8 s will result in loss of consciousness, while impairment of consciousness ensues when blood flow decreases to 25 mL/min per 100 g brain tissue.

From the clinical standpoint, a fall in systemic systolic blood pressure to ~50 mmHg or lower will result in syncope. A decrease in cardiac output and/or systemic vascular resistance—the determinants of blood pressure—thus underlies the pathophysiology of syncope. Common causes of impaired cardiac output include decreased effective circulating blood volume; increased thoracic pressure; massive pulmonary embolus; cardiac brady- and tachyarrhythmias; valvular heart disease; and myocardial dysfunction. Systemic vascular resistance may be decreased by central and peripheral autonomic nervous system diseases, sympatholytic medications, and transiently during neurally mediated syncope. Increased cerebral vascular resistance, most frequently due to hypocarbia induced by hyperventilation, may also contribute to the pathophysiology of syncope.

Two patterns of electroencephalographic (EEG) changes occur in syncopal subjects. The first is a "slow-flat-slow" pattern (Fig. 27-2) in which normal background activity is replaced with high-amplitude slow delta waves. This is followed by sudden flattening of the EEG—a cessation or attenuation of cortical activity—followed by the return of slow waves, and then normal activity. A second pattern, the "slow pattern," is characterized by increasing and decreasing slow wave activity only. The EEG flattening that occurs in the slow-flat-slow pattern is a marker of more severe cerebral hypoperfusion. Despite the presence of myoclonic movements and other motor activity during some syncopal events, EEG seizure discharges are not detected.

CLASSIFICATION

NEURALLY MEDIATED SYNCOPE

Neurally mediated (reflex; vasovagal) syncope is the final pathway of a complex central and peripheral nervous system reflex arc. There is a sudden, transient change in autonomic efferent activity with increased parasympathetic outflow, plus sympathoinhibition (the vasodepressor response), resulting in bradycardia, vasodilation, and/or reduced vasoconstrictor tone. The resulting fall in systemic blood pressure can then reduce cerebral blood flow to below the compensatory limits of autoregulation (Fig. 27-3). In order to elicit neutrally mediated syncope, a functioning autonomic nervous system is necessary, in contrast to syncope resulting from autonomic failure (discussed below).

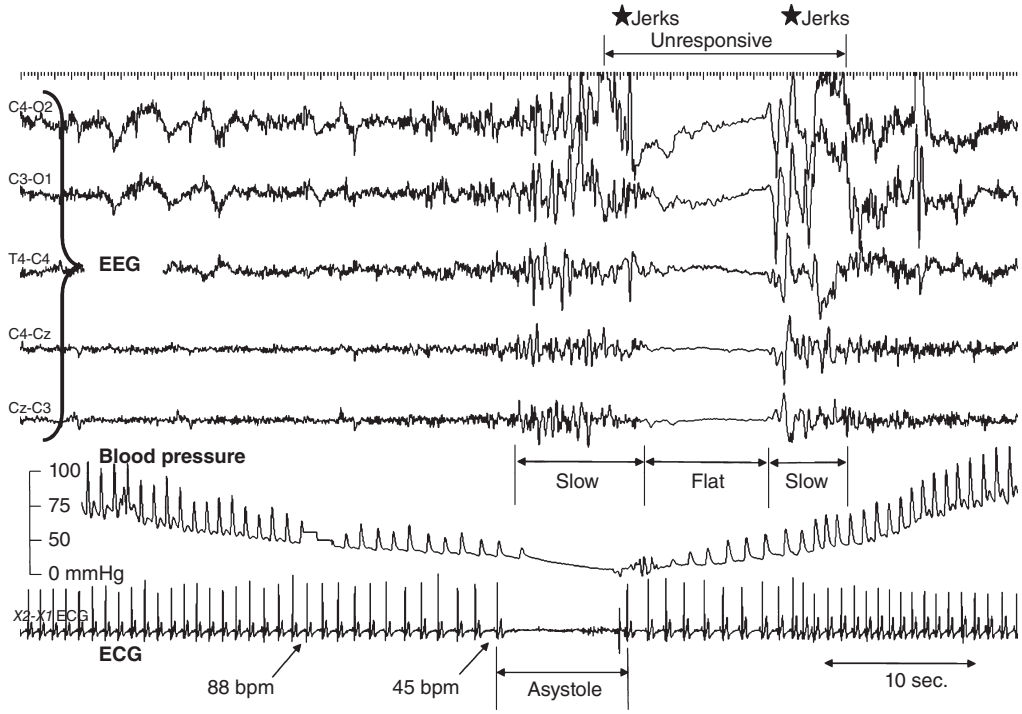

FIGURE 27-2 The electroencephalogram (EEG) in vasovagal syncope. A 1-min segment of a tilt-table test with typical vasovagal syncope demonstrating the "slow-flat-slow" EEG pattern. Finger beat-to-beat blood pressure, electrocardiogram (ECG), and selected EEG channels are shown. EEG slowing starts when systolic blood pressure drops to ~50 mmHg; heart rate is then approximately 45 beats/min (bpm). Asystole occurred, lasting about 8 s. The EEG flattens for a similar period, but with a delay. A transient loss of consciousness, lasting 14 s, was observed. There were muscle jerks just before and just after the flat period of the EEG. *(Figure reproduced with permission from W Wieling et al: Brain 132:2630, 2009.)*

Multiple triggers of the afferent limb of the reflex arc can result in neutrally mediated syncope. In some situations, these can be clearly defined, e.g., the carotid sinus, the gastrointestinal tract, or the bladder. Often, however, the trigger is less easily recognized and the cause is multifactorial. Under these circumstances, it is likely that different afferent pathways converge on the central autonomic network within the medulla that integrates the neural impulses and mediates the vasodepressor-bradycardic response.

Classification of Neurally Mediated Syncope Neurally mediated syncope may be subdivided based on the afferent pathway and provocative trigger. Vasovagal syncope (the common faint) is provoked by intense emotion, pain, and/or orthostatic stress, whereas the situational reflex syncopes have specific localized stimuli that provoke the reflex vasodilation and bradycardia that leads to syncope. The underlying mechanisms have been identified and pathophysiology delineated for most of these situational reflex syncopes. The afferent trigger may originate in the pulmonary system, gastrointestinal system, urogenital system, heart, and carotid artery (Table 27-2). Hyperventilation leading to hypocarbia and cerebral vasoconstriction, and raised intrathoracic pressure that impairs venous return to the heart, play a central role in many of the situational reflex syncopes. The afferent pathway of the reflex arc differs among these disorders, but the efferent response via the vagus and sympathetic pathways is similar.

Alternately, neurally mediated syncope may be subdivided based on the predominant efferent pathway. Vasodepressor syncope describes syncope predominantly due to efferent, sympathetic, vasoconstrictor failure; cardioinhibitory syncope describes syncope predominantly associated with bradycardia or asystole due

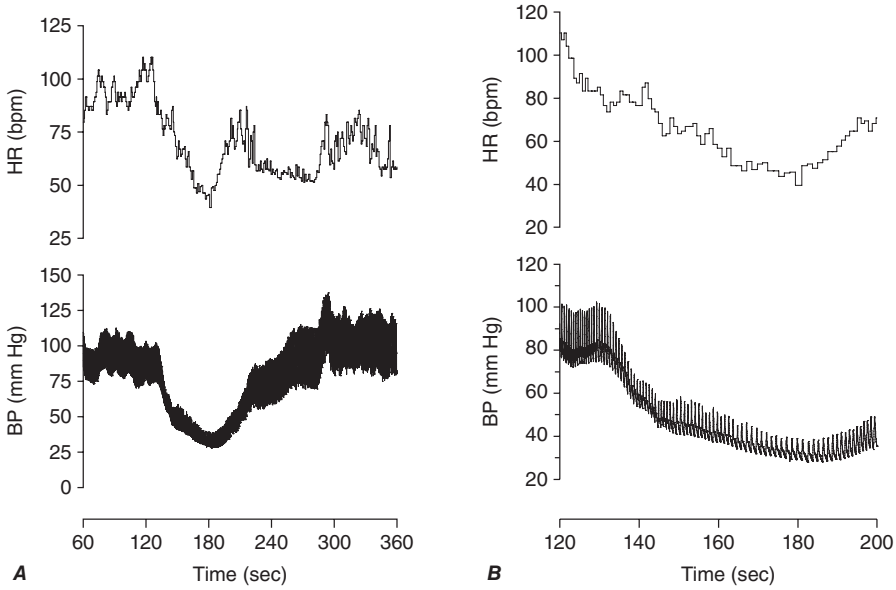

FIGURE 27-3 ***A.*** The paroxysmal hypotensive-bradycardic response that is characteristic of neurally mediated syncope. Noninvasive beat-to-beat blood pressure and heart rate are shown over 5 min (from 60 to 360 s) of an upright tilt on a tilt table. ***B.*** The same tracing expanded to show 80 s of the episode (from 80 to 200 s). BP, blood pressure; bpm, beats per minute; HR, heart rate.

TABLE 27-2 CAUSES OF SYNCOPE

A. Neurally Mediated Syncope

- Vasovagal syncope
  - Provoked fear, pain, anxiety, intense emotion, sight of blood, unpleasant sights and odors, orthostatic stress
- Situational reflex syncope
  - Pulmonary
    - Cough syncope, wind instrument player's syncope, weightlifter's syncope, "mess trick"[a] and "fainting lark,"[b] sneeze syncope, airway instrumentation
  - Urogenital
    - Postmicturition syncope, urogenital tract instrumentation, prostatic massage
  - Gastrointestinal
    - Swallow syncope, glossopharyngeal neuralgia, esophageal stimulation, gastrointestinal tract instrumentation, rectal examination, defecation syncope
  - Cardiac
    - Bezold-Jarisch reflex, cardiac outflow obstruction
  - Carotid sinus
    - Carotid sinus sensitivity, carotid sinus massage
  - Ocular
    - Ocular pressure, ocular examination, ocular surgery

B. Orthostatic Hypotension

- Primary autonomic failure due to idiopathic central and peripheral neurodegenerative diseases—the "synucleinopathies"
  - Lewy body diseases
    - Parkinson's disease
    - Lewy body dementia
    - Pure autonomic failure
  - Multiple system atrophy (the Shy-Drager syndrome)
- Secondary autonomic failure due to autonomic peripheral neuropathies
  - Diabetes
  - Hereditary amyloidosis (familial amyloid polyneuropathy)
  - Primary amyloidosis (AL amyloidosis; immunoglobulin light chain associated)
  - Hereditary sensory and autonomic neuropathies (HSAN) (especially type III—familial dysautonomia)
  - Idiopathic immune-mediated autonomic neuropathy
  - Autoimmune autonomic ganglionopathy
  - Sjögren's syndrome
  - Paraneoplastic autonomic neuropathy
  - HIV neuropathy
- Postprandial hypotension
- Iatrogenic (drug-induced)
- Volume depletion

C. Cardiac Syncope

- Arrhythmias
  - Sinus node dysfunction
  - Atrioventricular dysfunction
  - Supraventricular tachycardias
  - Ventricular tachycardias
  - Inherited channelopathies
- Cardiac structural disease
  - Valvular disease
  - Myocardial ischemia
  - Obstructive and other cardiomyopathies
  - Atrial myxoma
  - Pericardial effusions and tamponade

[a]Hyperventilation for ~1 minute, followed by sudden chest compression. [b]Hyperventilation (~20 breaths) in a squatting position, rapid rise to standing, then Valsalva.

to increased vagal outflow; and mixed syncope describes syncope in which there are both vagal and sympathetic reflex changes.

Features of Neurally Mediated Syncope In addition to symptoms of orthostatic intolerance such as dizziness, lightheadedness, and fatigue, premonitory features of autonomic activation may be present in patients with neurally mediated syncope. These include diaphoresis, pallor, palpitations, nausea, hyperventilation, and yawning. During the syncopal event, proximal and distal myoclonus (typically arrhythmic and multifocal) may occur, raising the possibility of epilepsy. The eyes typically remain open and usually deviate upward. Pupils are usually dilated. Roving eye movements may occur. Grunting, moaning, snorting, and stertorous breathing may be present. Urinary incontinence may occur. Fecal incontinence is very rare. Postictal confusion is also rare, although visual and auditory hallucinations and near death and out-of-body experiences are sometimes reported.

Although some predisposing factors and provocative stimuli are well established (for example, motionless upright posture, warm ambient temperature, intravascular volume depletion, alcohol ingestion, hypoxemia, anemia, pain, the sight of blood, venipuncture, and intense emotion), the underlying basis for the widely different thresholds for syncope among individuals exposed to the same provocative stimulus is not known. A genetic basis for neurally mediated syncope may exist; several studies have reported an increased incidence of syncope in first-degree relatives of fainters, but no gene or genetic marker has been identified, and environmental, social, and cultural factors have not been excluded by these studies.

TREATMENT NEURALLY MEDIATED SYNCOPE

Reassurance, avoidance of provocative stimuli, and plasma volume expansion with fluid and salt are the cornerstones of the management of neurally mediated syncope. Isometric counterpressure maneuvers of the limbs (leg crossing or handgrip and arm tensing) may raise blood pressure by increasing central blood volume and cardiac output. By maintaining pressure in the autoregulatory zone, these maneuvers avoid or delay the onset of syncope. Randomized controlled trials support this intervention.

Fludrocortisone, vasoconstricting agents, and beta-adrenoreceptor antagonists are widely used by experts to treat refractory patients, although there is no consistent evidence from randomized controlled trials for any pharmacotherapy to treat neurally mediated syncope. Because vasodilation is the dominant pathophysiologic syncopal mechanism in most patients, use of a cardiac pacemaker is rarely beneficial. Possible exceptions are older patients (>40 years) in whom syncope is associated with asystole or severe bradycardia and patients with prominent cardioinhibition due to carotid sinus syndrome. In these patients, dual-chamber pacing may be helpful.

ORTHOSTATIC HYPOTENSION

Orthostatic hypotension, defined as a reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 min of standing or head-up tilt on a tilt table, is a manifestation of sympathetic vasoconstrictor (autonomic) failure (Fig. 27-4). In many (but not all) cases, there is no compensatory increase in heart rate despite hypotension; with partial autonomic failure, heart rate may increase to some degree but is insufficient to maintain cardiac output. A variant of orthostatic hypotension is "delayed" orthostatic hypotension, which occurs beyond 3 min of standing; this may reflect a mild or early form of sympathetic adrenergic dysfunction. In some cases, orthostatic hypotension occurs within 15 s of standing (so-called "initial" orthostatic hypotension), a finding that may reflect a transient mismatch between cardiac output and peripheral vascular resistance and does not represent autonomic failure.

Characteristic symptoms of orthostatic hypotension include lightheadedness, dizziness, and presyncope (near-faintness) occurring in response to sudden postural change. However, symptoms may be

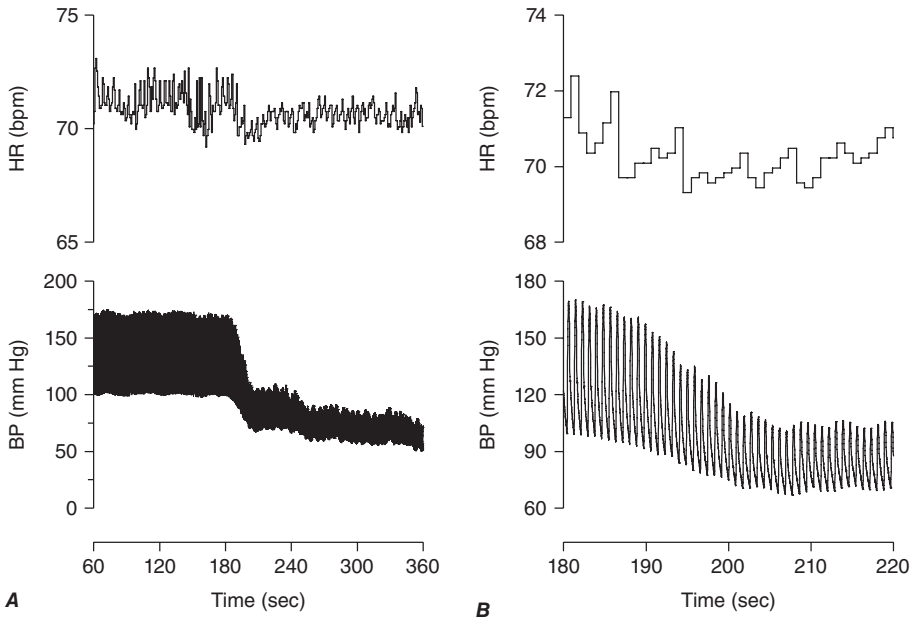

FIGURE 27-4 ***A.*** The gradual fall in blood pressure without a compensatory heart rate increase that is characteristic of orthostatic hypotension due to autonomic failure. Blood pressure and heart rate are shown over 5 min (from 60 to 360 s) of an upright tilt on a tilt table. ***B.*** The same tracing expanded to show 40 s of the episode (from 180 to 220 s). BP, blood pressure; bpm, beats per minute; HR, heart rate.

absent or nonspecific, such as generalized weakness, fatigue, cognitive slowing, leg buckling, or headache. Visual blurring may occur, likely due to retinal or occipital lobe ischemia. Neck pain, typically in the suboccipital, posterior cervical, and shoulder region (the "coat-hanger headache"), most likely due to neck muscle ischemia, may be the only symptom. Patients may report orthostatic dyspnea (thought to reflect ventilation-perfusion mismatch due to inadequate perfusion of ventilated lung apices) or angina (attributed to impaired myocardial perfusion even with normal coronary arteries). Symptoms may be exacerbated by exertion, prolonged standing, increased ambient temperature, or meals. Syncope is usually preceded by warning symptoms, but may occur suddenly, suggesting the possibility of a seizure or cardiac cause.

Supine hypertension is common in patients with orthostatic hypotension due to autonomic failure, affecting over 50% of patients in some series. Orthostatic hypotension may present after initiation of therapy for hypertension, and supine hypertension may follow treatment of orthostatic hypotension. However, in other cases, the association of the two conditions is unrelated to therapy; it may in part be explained by baroreflex dysfunction in the presence of residual sympathetic outflow, particularly in patients with central autonomic degeneration.

Causes of Neurogenic Orthostatic Hypotension Causes of neurogenic orthostatic hypotension include central and peripheral autonomic nervous system dysfunction (Chap. 454). Autonomic dysfunction of other organ systems (including the bladder, bowels, sexual organs, and sudomotor system) of varying severity frequently accompanies orthostatic hypotension in these disorders (Table 27-2).

The primary autonomic degenerative disorders are multiple system atrophy (the Shy-Drager syndrome; Chap. 454), Parkinson's disease (Chap. 449), dementia with Lewy bodies (Chap. 448), and pure autonomic failure (Chap. 454). These are often grouped together as "synucleinopathies" due to the presence of alpha-synuclein, a small protein that precipitates predominantly in the cytoplasm of neurons in the Lewy body disorders (Parkinson's disease, dementia with Lewy bodies, and pure autonomic failure) and in the glia in multiple system atrophy.

Peripheral autonomic dysfunction may also accompany small-fiber peripheral neuropathies such as those seen in diabetes, amyloid, immune-mediated neuropathies, hereditary sensory and autonomic neuropathies (HSAN; particularly HSAN type III, familial dysautonomia), and inflammatory neuropathies (Chaps. 459 and 460). Less frequently, orthostatic hypotension is associated with the peripheral neuropathies that accompany vitamin B_{12} deficiency, neurotoxic exposure, HIV and other infections, and porphyria.

Patients with autonomic failure and the elderly are susceptible to falls in blood pressure associated with meals. The magnitude of the blood pressure fall is exacerbated by large meals, meals high in carbohydrate, and alcohol intake. The mechanism of postprandial syncope is not fully elucidated.

Orthostatic hypotension is often iatrogenic. Drugs from several classes may lower peripheral resistance (e.g., alpha-adrenoreceptor antagonists used to treat hypertension and prostatic hypertrophy; antihypertensive agents of several classes; nitrates and other vasodilators; tricyclic agents and phenothiazines). Iatrogenic volume depletion due to diuresis and volume depletion due to medical causes (hemorrhage, vomiting, diarrhea, or decreased fluid intake) may also result in decreased effective circulatory volume, orthostatic hypotension, and syncope.

TREATMENT **ORTHOSTATIC HYPOTENSION**

The first step is to remove reversible causes—usually vasoactive medications (Table 454-6). Next, nonpharmacologic interventions should be introduced. These interventions include patient education regarding staged moves from supine to upright; warnings about the hypotensive effects of large meals; instructions about the isometric counterpressure maneuvers that increase intravascular pressure (see above); and raising the head of the bed to reduce supine hypertension. Intravascular volume should be expanded by increasing dietary fluid and salt. If these nonpharmacologic measures fail, pharmacologic intervention with fludrocortisone acetate and vasoconstricting agents such as midodrine, L-dihydroxyphenylserine, and pseudoephedrine should be introduced. Some patients with intractable symptoms require additional therapy with supplementary agents that include pyridostigmine, yohimbine, desmopressin acetate (DDAVP), and erythropoietin (Chap. 454).

CARDIAC SYNCOPE

Cardiac (or cardiovascular) syncope is caused by arrhythmias and structural heart disease. These may occur in combination because structural disease renders the heart more vulnerable to abnormal electrical activity.

Arrhythmias Bradyarrhythmias that cause syncope include those due to severe sinus node dysfunction (e.g., sinus arrest or sinoatrial block) and atrioventricular (AV) block (e.g., Mobitz type II, high-grade, and complete AV block). The bradyarrhythmias due to sinus node dysfunction are often associated with an atrial tachyarrhythmia, a disorder known as the tachycardia-bradycardia syndrome. A prolonged pause following the termination of a tachycardic episode is a frequent cause of syncope in patients with the tachycardia-bradycardia syndrome. Medications of several classes may also cause bradyarrhythmias of sufficient severity to cause syncope. Syncope due to bradycardia or asystole is referred to as a Stokes-Adams attack.

Ventricular tachyarrhythmias frequently cause syncope. The likelihood of syncope with ventricular tachycardia is in part dependent on

the ventricular rate; rates below 200 beats/min are less likely to cause syncope. The compromised hemodynamic function during ventricular tachycardia is caused by ineffective ventricular contraction, reduced diastolic filling due to abbreviated filling periods, loss of AV synchrony, and concurrent myocardial ischemia.

Several disorders associated with cardiac electrophysiologic instability and arrhythmogenesis are due to mutations in ion channel subunit genes. These include the long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. The long QT syndrome is a genetically heterogeneous disorder associated with prolonged cardiac repolarization and a predisposition to ventricular arrhythmias. Syncope and sudden death in patients with long QT syndrome result from a unique polymorphic ventricular tachycardia called *torsades des pointes* that degenerates into ventricular fibrillation. The long QT syndrome has been linked to genes encoding K^+ channel α-subunits, K^+ channel β-subunits, voltage-gated Na^+ channel, and a scaffolding protein, ankyrin B (ANK2). Brugada syndrome is characterized by idiopathic ventricular fibrillation in association with right ventricular electrocardiogram (ECG) abnormalities without structural heart disease. This disorder is also genetically heterogeneous, although it is most frequently linked to mutations in the Na^+ channel α-subunit, SCN5A. Catecholaminergic polymorphic tachycardia is an inherited, genetically heterogeneous disorder associated with exercise- or stress-induced ventricular arrhythmias, syncope, or sudden death. Acquired QT interval prolongation, most commonly due to drugs, may also result in ventricular arrhythmias and syncope. **These disorders are discussed in detail in Chap. 277.**

Structural Disease Structural heart disease (e.g., valvular disease, myocardial ischemia, hypertrophic and other cardiomyopathies, cardiac masses such as atrial myxoma, and pericardial effusions) may lead to syncope by compromising cardiac output. Structural disease may also contribute to other pathophysiologic mechanisms of syncope. For example, cardiac structural disease may predispose to arrhythmogenesis; aggressive treatment of cardiac failure with diuretics and/or vasodilators may lead to orthostatic hypotension; and inappropriate reflex vasodilation may occur with structural disorders such as aortic stenosis and hypertrophic cardiomyopathy, possibly provoked by increased ventricular contractility.

TREATMENT CARDIAC SYNCOPE

Treatment of cardiac disease depends on the underlying disorder. Therapies for arrhythmias include cardiac pacing for sinus node disease and AV block, and ablation, antiarrhythmic drugs, and cardioverter-defibrillators for atrial and ventricular tachyarrhythmias. These disorders are best managed by physicians with specialized skills in this area.

APPROACH TO THE PATIENT: Syncope

DIFFERENTIAL DIAGNOSIS

Syncope is easily diagnosed when the characteristic features are present; however, several disorders with transient real or apparent loss of consciousness may create diagnostic confusion.

Generalized and partial seizures may be confused with syncope; however, there are a number of differentiating features. Whereas tonic-clonic movements are the hallmark of a generalized seizure, myoclonic and other movements also may occur in up to 90% of syncopal episodes. Myoclonic jerks associated with syncope may be multifocal or generalized. They are typically arrhythmic and of short duration (<30 s). Mild flexor and extensor posturing also may occur. Partial or partial-complex seizures with secondary generalization are usually preceded by an aura, commonly an unpleasant smell; fear; anxiety; abdominal discomfort; or other visceral sensations. These phenomena should be differentiated from the premonitory features of syncope.

Autonomic manifestations of seizures (autonomic epilepsy) may provide a more difficult diagnostic challenge. Autonomic seizures have cardiovascular, gastrointestinal, pulmonary, urogenital, pupillary, and cutaneous manifestations that are similar to the premonitory features of syncope. Furthermore, the cardiovascular manifestations of autonomic epilepsy include clinically significant tachycardias and bradycardias that may be of sufficient magnitude to cause loss of consciousness. The presence of accompanying nonautonomic auras may help differentiate these episodes from syncope.

Loss of consciousness associated with a seizure usually lasts longer than 5 min and is associated with prolonged postictal drowsiness and disorientation, whereas reorientation occurs almost immediately after a syncopal event. Muscle aches may occur after both syncope and seizures, although they tend to last longer and be more severe following a seizure. Seizures, unlike syncope, are rarely provoked by emotions or pain. Incontinence of urine may occur with both seizures and syncope; however, fecal incontinence occurs very rarely with syncope.

Hypoglycemia may cause transient loss of consciousness, typically in individuals with type 1 or type 2 diabetes treated with insulin. The clinical features associated with impending or actual hypoglycemia include tremor, palpitations, anxiety, diaphoresis, hunger, and paresthesias. These symptoms are due to autonomic activation to counter the falling blood glucose. Hunger, in particular, is not a typical premonitory feature of syncope. Hypoglycemia also impairs neuronal function, leading to fatigue, weakness, dizziness, and cognitive and behavioral symptoms. Diagnostic difficulties may occur in individuals in strict glycemic control; repeated hypoglycemia impairs the counterregulatory response and leads to a loss of the characteristic warning symptoms that are the hallmark of hypoglycemia.

Patients with cataplexy experience an abrupt partial or complete loss of muscular tone triggered by strong emotions, typically anger or laughter. Unlike syncope, consciousness is maintained throughout the attacks, which typically last between 30 s and 2 min. There are no premonitory symptoms. Cataplexy occurs in 60–75% of patients with narcolepsy.

The clinical interview and interrogation of eyewitnesses usually allow differentiation of syncope from falls due to vestibular dysfunction, cerebellar disease, extrapyramidal system dysfunction, and other gait disorders. If the fall is accompanied by head trauma, a postconcussive syndrome, amnesia for the precipitating events, and/or the presence of loss of consciousness may contribute to diagnostic difficulty.

Apparent loss of consciousness can be a manifestation of psychiatric disorders such as generalized anxiety, panic disorders, major depression, and somatization disorder. These possibilities should be considered in individuals who faint frequently without prodromal symptoms. Such patients are rarely injured despite numerous falls. There are no clinically significant hemodynamic changes concurrent with these episodes. In contrast, transient loss of consciousness due to vasovagal syncope precipitated by fear, stress, anxiety, and emotional distress is accompanied by hypotension, bradycardia, or both.

INITIAL EVALUATION

The goals of the initial evaluation are to determine whether the transient loss of consciousness was due to syncope; to identify the cause; and to assess risk for future episodes and serious harm (Table 27-1). The initial evaluation should include a detailed history, thorough questioning of eyewitnesses, and a complete physical and neurologic examination. Blood pressure and heart rate should be measured in the supine position and after 3 min of standing to determine whether orthostatic hypotension is present. An ECG should be performed if there is suspicion of syncope due to an arrhythmia or underlying cardiac disease. Relevant electrocardiographic abnormalities include bradyarrhythmias or tachyarrhythmias, AV block, ischemia, old myocardial infarction, long QT syndrome, and bundle branch block. This initial assessment will lead to the identification of a cause of syncope in approximately

50% of patients and also allows stratification of patients at risk for cardiac mortality.

Laboratory Tests Baseline laboratory blood tests are rarely helpful in identifying the cause of syncope. Blood tests should be performed when specific disorders, e.g., myocardial infarction, anemia, and secondary autonomic failure, are suspected (Table 27-2).

Autonomic Nervous System Testing (Chap. 454) Autonomic testing, including tilt-table testing, can be performed in specialized centers. Autonomic testing is helpful to uncover objective evidence of autonomic failure and also to demonstrate a predisposition to neurally mediated syncope. Autonomic testing includes assessments of parasympathetic autonomic nervous system function (e.g., heart rate variability to deep respiration and a Valsalva maneuver), sympathetic cholinergic function (e.g., thermoregulatory sweat response and quantitative sudomotor axon reflex test), and sympathetic adrenergic function (e.g., blood pressure response to a Valsalva maneuver and a tilt-table test with beat-to-beat blood pressure measurement). The hemodynamic abnormalities demonstrated on tilt-table test (Figs. 27-3 and 27-4) may be useful in distinguishing orthostatic hypotension due to autonomic failure from the hypotensive bradycardic response of neurally mediated syncope. Similarly, the tilt-table test may help identify patients with syncope due to immediate or delayed orthostatic hypotension.

Carotid sinus massage should be considered in patients with symptoms suggestive of carotid sinus syncope and in patients over age 50 years with recurrent syncope of unknown etiology. This test should only be carried out under continuous ECG and blood pressure monitoring and should be avoided in patients with carotid bruits, plaques, or stenosis.

Cardiac Evaluation ECG monitoring is indicated for patients with a high pretest probability of arrhythmia causing syncope. Patients should be monitored in hospital if the likelihood of a life-threatening arrhythmia is high, e.g., patients with severe structural or coronary artery disease, nonsustained ventricular tachycardia, trifascicular heart block, prolonged QT interval, Brugada syndrome ECG pattern, or family history of sudden cardiac death (Table 27-1). Outpatient Holter monitoring is recommended for patients who experience frequent syncopal episodes (one or more per week), whereas loop recorders, which continually record and erase cardiac rhythm, are indicated for patients with suspected arrhythmias with low risk of sudden cardiac death. Loop recorders may be external (recommended for evaluation of episodes that occur at a frequency of greater than one per month) or implantable (if syncope occurs less frequently).

Echocardiography should be performed in patients with a history of cardiac disease or if abnormalities are found on physical examination or the ECG. Echocardiographic diagnoses that may be responsible for syncope include aortic stenosis, hypertrophic cardiomyopathy, cardiac tumors, aortic dissection, and pericardial tamponade. Echocardiography also has a role in risk stratification based on the left ventricular ejection fraction.

Treadmill exercise testing with ECG and blood pressure monitoring should be performed in patients who have experienced syncope during or shortly after exercise. Treadmill testing may help identify exercise-induced arrhythmias (e.g., tachycardia-related AV block) and exercise-induced exaggerated vasodilation.

Electrophysiologic studies are indicated in patients with structural heart disease and ECG abnormalities in whom noninvasive investigations have failed to yield a diagnosis. Electrophysiologic studies have low sensitivity and specificity and should only be performed when a high pretest probability exists. Currently, this test is rarely performed to evaluate patients with syncope.

Psychiatric Evaluation Screening for psychiatric disorders may be appropriate in patients with recurrent unexplained syncope episodes. Tilt-table testing, with demonstration of symptoms in the absence of hemodynamic change, may be useful in reproducing syncope in patients with suspected psychogenic syncope.

28 Dizziness and Vertigo

Mark F. Walker, Robert B. Daroff

Dizziness is an imprecise symptom used to describe a variety of sensations that include vertigo, light-headedness, faintness, and imbalance. When used to describe a sense of spinning or other motion, dizziness is designated as *vertigo*. Vertigo may be physiologic, occurring during or after a sustained head rotation, or it may be pathologic, due to vestibular dysfunction. The term *light-headedness* is commonly applied to presyncopal sensations due to brain hypoperfusion but also may refer to disequilibrium and imbalance. A challenge to diagnosis is that patients often have difficulty distinguishing among these various symptoms, and the words they choose do not reliably indicate the underlying etiology.

There are a number of potential causes of dizziness. Vascular disorders cause presyncopal dizziness as a result of cardiac dysrhythmia, orthostatic hypotension, medication effects, or other causes. Such presyncopal sensations vary in duration; they may increase in severity until loss of consciousness occurs, or they may resolve before loss of consciousness if the cerebral ischemia is corrected. Faintness and syncope, which are discussed in detail in Chap. 27, should always be considered when one is evaluating patients with brief episodes of dizziness or dizziness that occurs with upright posture.

Vestibular causes of dizziness (vertigo or imbalance) may be due to peripheral lesions that affect the labyrinths or vestibular nerves or to involvement of the central vestibular pathways. They may be paroxysmal or due to a fixed unilateral or bilateral vestibular deficit. Acute unilateral lesions cause vertigo due to a sudden imbalance in vestibular inputs from the two labyrinths. Bilateral lesions cause imbalance and instability of vision (*oscillopsia*) when the head moves. Other causes of dizziness include nonvestibular imbalance and gait disorders (e.g., loss of proprioception from sensory neuropathy, parkinsonism) and anxiety.

When evaluating patients with dizziness, questions to consider include the following: (1) Is it dangerous (e.g., arrhythmia, transient ischemic attack/stroke)? (2) Is it vestibular? (3) If vestibular, is it peripheral or central? A careful history and examination often provide sufficient information to answer these questions and determine whether additional studies or referral to a specialist is necessary.

APPROACH TO THE PATIENT: Dizziness

HISTORY

When a patient presents with dizziness, the first step is to delineate more precisely the nature of the symptom. In the case of vestibular disorders, the physical symptoms depend on whether the lesion is unilateral or bilateral, and whether it is acute or chronic and progressive. Vertigo, an illusion of self or environmental motion, implies asymmetry of vestibular inputs from the two labyrinths or in their central pathways that is usually acute. Symmetric bilateral vestibular hypofunction causes imbalance but no vertigo. Because of the ambiguity in patients' descriptions of their symptoms, diagnosis based simply on symptom characteristics is typically unreliable. The history should focus closely on other features, including whether this is the first attack, the duration of this and any prior episodes, provoking factors, and accompanying symptoms.

Dizziness can be divided into episodes that last for seconds, minutes, hours, or days. Common causes of brief dizziness (seconds) include benign paroxysmal positional vertigo (BPPV) and orthostatic hypotension, both of which typically are provoked by changes in head and body position. Attacks of vestibular migraine and Ménière's disease often last hours. When episodes are of intermediate duration (minutes), transient ischemic attacks of the posterior circulation should be considered, although migraine and a number of other causes are also possible.